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Skeletal Scintigraphy

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Skeletal scintigraphy, using phosphates or diphosphonates labeled with technetium 99m, is a sensitive method of detecting bone abnormalities. The most important and most frequent role of bone scanning is evaluating the skeletal areas in patients who have a primary cancer, especially a malignant condition that has a tendency to spread to bone areas. The bone scan is superior to bone radiographs in diagnosing these abnormalities; 15 percent to 25 percent of patients with breast, prostate or lung cancer, who have normal roentgenograms, also have abnormal scintigrams due to metastases. The majority of bone metastases appear as hot spots on the scan and are easily recognized. The incidence of abnormal bone scans in patients with early stages (I and II) of breast cancer varies from 6 percent to 26 percent, but almost invariably those patients with scan abnormalities have a poor prognosis and should be considered for additional therapies. Progression or regression of bony lesions can be defined through scanning, and abnormal areas can be identified for biopsy. The incidence of metastases in solitary scan lesions in patients with known primary tumors varies from 20 percent to 64 percent. Bone scintigraphy shows positive uptake in 95 percent of cases with acute osteomyelitis. Stress fractures and trauma suspected in battered babies can be diagnosed by scanning before there is radiological evidence. The procedure is free from acute or long-term side effects and, except in cases of very young patients, sedation is seldom necessary.

Although the test is sensitive, it is not specific and therefore it is difficult to overemphasize the importance of clinical, radiographic, biochemical and scanning correlation in each patient.

SKELETAL SCINTIGRAPHY, bone scanning, is one of the most important tests in nuclear medicine. There are two main reasons for this: first, the availability of a variety of bone-seeking phosphate and diphosphonate compounds which can be conveniently and efficiently labeled with technetium 99m; and second, the development of detecting devices which are capable of producing high resolution, whole body images. The benefits of the agents labeled with ^{99m}Tc are that they produce a low radiation dose in patients, their half-lives are convenient for producing images two to four hours after their administration, and the monoenergetic gamma ray (140 keV) is ideal for current imaging devices. Whole body images allow all bones to be evaluated, a task diagnostic radiologists do not undertake with equanimity. Some centers have instruments capable of producing

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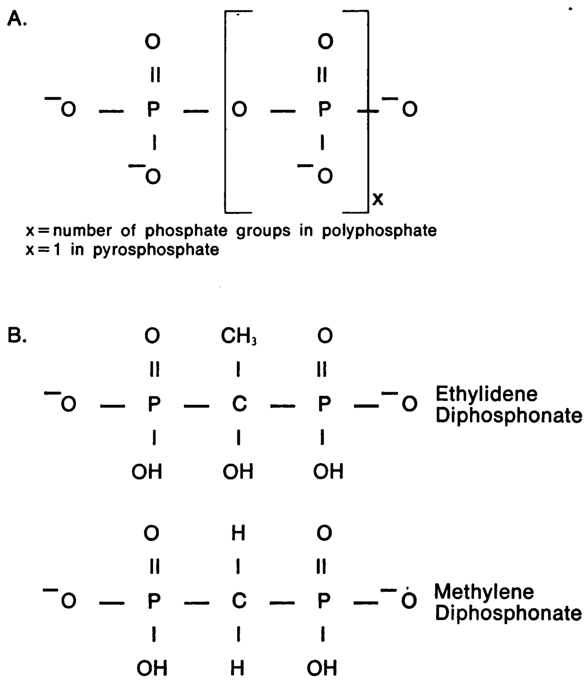

Figure 1.—Structure of phosphates and phosphonates

whole body tomographic images, from which the depth of lesions can be evaluated.

This article will deal with the pharmacology of the bone scanning agents and some important aspects of methodology. The value of bone scanning in patients with cancer will be described, with particular emphasis on breast and prostate cancer. There will follow sections on the use of bone scintigraphy in infectious diseases of the skeleton and in various metabolic bone disorders. A section is devoted to *benign* bone disorders including osteonecrosis and trauma. Nonskeletal disorders seen on bone scan and finally artifacts will be discussed. Joint diseases are not described in this article.

Radiopharmaceutical Agents and Pharmacokinetics

There are several phosphate and phosphonate compounds that can be labeled with ^{99m}Tc. The phosphates include pyrophosphate, polyphosphate[1] and monfluorophosphate.[2] They have the basic structure shown in Figure 1A. Phosphonates include hydroxy-ethylidene diphosphonate[3,4] and methylene diphosphonate; their structure is shown in Figure 1B. All of these compounds are available in commercial kits which can be labeled simply and efficiently *in vitro* with ^{99m}Tc. There are some minor differences in the distribution of these agents after intravenous injection *in vivo.* In general, the phosphonates are cleared from the blood more rapidly by the kidneys and about 60 percent to 70 percent of the material is found in the urine in six hours.[5] The more rapid renal clearance of phosphonates produces a more intense ratio of bone to the background and in some cases a higher ratio of tumor to bone. Therefore, phosphonate scans are easier to interpret. Many investigators agree that the image obtained with diphosphonates is superior to that obtained with phosphates[6] and there is clinical information to suggest that when both agents are compared in the same patient additional lesions are seen in diphosphonate scans.[7,8] Methylene diphosphonate produces a higher ratio of bone to background than ethylidene diphosphonate at all intervals between a half hour to five hours, but it has yet to be shown that additional lesions are detected with this agent.[9,10]

The risk of toxicity from these agents is extremely small in view of the small doses of pharmaceutical agents used[11] and the author is unaware of any clinical or metabolic problems that could be attributed to them.

The phosphate and phosphonates attach to hyroxyapatite crystals through a combination of physical and chemical methods (chemisorption). This leads to the question of increased uptake in abnormal areas such as carcinoma or abscess. The most important factor is blood flow to the bones; increased blood flow to lesions is responsible for increased uptake. A second factor is increased metabolic activity in reactive bone-surrounding lesions, which is less likely because the radiopharmaceutical agent is not primarily in bone cells.

Methods

Bone scans are made about three hours after the intravenous injection of the bone scanning agent. Snow and Weber[12] compared normal and abnormal bone areas with soft tissue in a detailed study using pyrophosphate. They showed that a delay of three to four hours is optimal. In contrast, Potsaid and co-workers[13] believed there was no loss in quality if imaging was conducted at two hours; however, they used diphosphonate. Curtailing the time between injection and scanning to less than two hours is unwise, because the higher background level of radioactivity reduces the quality of the image.

Under certain circumstances there is an advantage in delaying the scan longer than four hours after injection of the radiopharmaceutical agent.[14] If a proportion of the agent is infiltrated at the time of injection there is a gradual resorption of radioactivity from this site, which causes a higher background, and waiting for six hours frequently produces a better image. If bladder activity makes assessment of the pelvis difficult, even when images are made immediately after micturition, a delay of 24 hours will greatly reduce the bladder contribution.[15] In a study comparing 4-hour and 24-hour bone scans, lesions were enhanced in 13 of 23 patients in the delayed scan: in fact in five patients, abnormalities not seen at four hours became apparent at the later time. The longer the image is delayed, the less radioactivity will be present and the longer the scanning will take.[16]

Each study of a patient has to be evaluated in the context of the clinical problem to be answered. In the majority of patients the scan will be made between two and four hours after injection of the radiopharmaceutical agent.

It is common for spot films to be obtained of areas that appear suspicious on whole body scans. These help determine whether or not a true abnormality is present and are useful in planning biopsy sites and radiotherapy treatment ports. Marking of scan abnormalities for bone biopsy requires meticulous attention and close cooperation between the nuclear physician and the surgeon, who should be present when skin markers, overlying a bony abnormality, are placed.

Under most circumstances, unprocessed bone scans provide all the information the referring physician requires. Several groups of investigators have evaluated quantitation of scans by comparing the uptake of radioactivity in lesions with that in normal bone, or soft tissue.[17-20] This requires the camera to be interfaced with a computer, so that areas of interest can be outlined and count rates within these areas can be measured. A numerical result is obtained from this information and this number can be used for comparison with the numerical result from the same region in subsequent scans. It remains to be seen whether this type of quantitation will provide additional clinically useful information.

In adults, the administered dose of ^{99m}Tc is in the range of 15 to 25 MCi and in children correspondingly lower doses are based on age and weight. Patients of all ages can be evaluated, but in the younger-age groups it may be necessary to have a hypnotic prescribed before attempting the scan. In children it is also wise to inject the radiopharmaceutical agent through an indwelling catheter; this makes the procedure less traumatic for both patient and physician, and also prevents infiltration of the material.

The distribution of a radiopharmaceutical agent is symmetrical in persons without abnormalities. The area with most intense uptake in adults is the axial skeleton. In children it is the metaphyses of long bones. The quality of image deteriorates as the age of the patient increases, and as the thickness of adipose tissue increases. There are variations in normal findings which can only be recognized by reviewing large numbers of scans with knowledge of each patient's history, review of appropriate roentgenograms and subsequent follow-up studies. This article does not dwell on the normal bone scan; Figures 2 and 3, however, show normal scans in an adult and in a child, respectively.

Bone Scanning in Patients With Malignant Disease

Carcinoma of the breast, lung, prostate, kidney and thyroid metastasize to bone areas. The first three are common types of cancer and the occurrence of skeletal metastases significantly alters the prognoses. There are now numerous studies confirming that bone scanning is more sensitive than roentgenograms in evaluating the presence of metastatic lesions.[21-25] In most cases multiple abnormalities of the axial skeleton and ribs, and the pattern of these abnormalities, make the diagnosis of metastasis most likely. Scans are more sensitive than roentgenograms because 50 percent of bone mineral content must be lost before a lesion is radiographically visible,[26] and the scan depends on different factors for positive uptake.

The indications for bone scanning in patients with cancer are: (1) to determine that no metastases are present and (2) to determine the presence of metastases. In ideal circumstances it would be advantageous to have the scan interpreted before surgical operation on the primary lesion is done, because the presence of metastatic lesions might make a major difference in the extent of the procedure. This would be especially true of cancer of the lung, in which the presence of bone metastasis might be considered a reason to cancel surgical treatment. On the other hand, many lesions in the breast are benign and it would be unjustifiable to obtain preoperative scans in all patients in whom breast lumps are to be re-

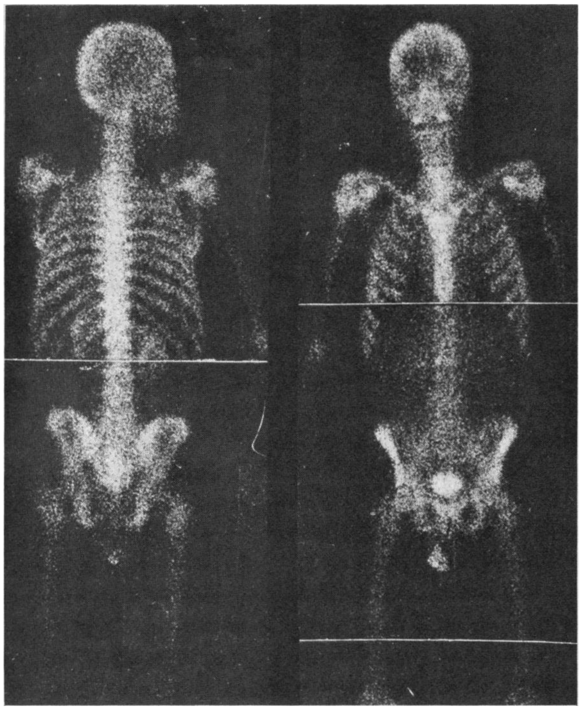

Figure 2.—Anterior and posterior images of the skeleton in a 37-year-old man. Normal distribution of methylene diphosphonate labeled with technetium 99m showing homogeneous symmetrical activity in the axial skeleton.

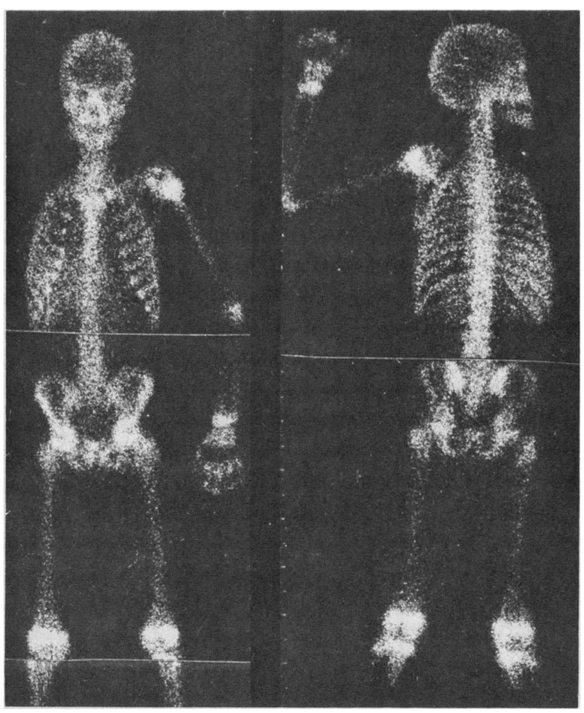

Figure 3.—Posterior and anterior images in a 12-year-old boy who had a right arm disarticulated for treatment of osteogenic sarcoma. The scan is otherwise normal and compared with Figure 1 shows more intense uptake in the growing ends of long bones.

moved. In patients considered most likely to have cancer of the breast, a preoperative scan would be appropriate to (1) define the optimal place for bone biopsy, (2) record progression or regression of disease, (3) provide prognostic information and (4) obtain data about the natural history of cancers with and without bony metastasis.

As far as is possible, from published information, these points will be discussed below.

Breast Cancer

The prevalence of bone metastases on scans from patients with cancer of the breast varies considerably among published reports. It is not possible to explain these differences on the basis of different radiopharmaceutical agents, imaging techniques or detecting equipment. Most likely the differences are related to different patient populations being evaluated.

Campbell and associates[27] found abnormal scans in 26 percent of 80 patients; 18 percent of the abnormal scans were from patients with stage I cancer, and 41 percent in patients with stage II. The site of the breast lesion, or its size, did not correlate with the presence of metastatic lesions; however, there was a high correlation between the presence of these lesions in axillary nodes and an abnormal scan. After 12 months, 54 percent of the patients with abnormal scans had clinical evidence of disseminated disease, compared with 5.7 percent of the patients with normal scans. In a series of 192 patients, abnormal scans were found in only nine patients (5 percent); systemic disease developed in eight (88 percent) of the nine patients and four died. Nine of the 183 patients whose scans were originally normal subsequently had abnormal scans (5 percent).[28] In 50 patients with early cancer of the breast Galasko[29] found bone metastases in 12 (24 percent) who had normal roentgenograms. Disseminated disease developed in all of them and ten patients (83 percent) died within five years. These findings contrasted with the five-year mortality of 34 percent of the patients with normal scans. Citrin and associates[30] conducted a study using sequential scans in 75 patients with stage I or stage II cancer of the breast. Scans from 11 patients (14 percent) showed evidence of metastases and scans from 13 patients changed from normal to abnormal in the course of the study. These patients did poorly whereas only one of 51 patients who had persistently normal scans died. Gerber and coworkers[31] found bone metastases in only 6 percent

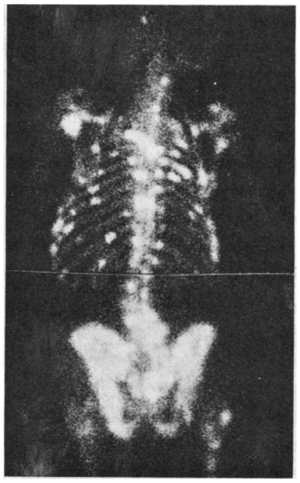

Figure 4.—Multiple abnormalities appearing as areas of intense uptake in a patient with metastatic cancer of the prostate.

of 122 patients, but noted a change from normal to abnormal within three months in some patients.

A varying proportion of patients with early primary cancer of the breast (stage I or II) have lesions seen on bone scans (6 percent to 26 percent). A greater percentage of those with advanced cancer of the breast have bone scan findings consistent with metastases. The scan is useful in determining the stages of cancer.[32] Patients with bone metastases, as well as those patients whose bone scan changes from normal to abnormal, have a poor prognosis. It would seem that patients with abnormal scans should be considered for additional therapy, which would be dictated by other factors such as age, menstrual status and estrogen receptor status of the cancer.

Prostate Cancer

Prostate cancer, the most common cancer in men, has a strong tendency to spread to bone areas and the bone scan appearance of metastases in this condition is frequently striking (Figure 4).

In a review of 219 patients, 43 percent of those with proven metastases to the bone and an abnormal scan had no bone pain, 39 percent had normal levels of acid phosphatase and 23 percent had normal values for alkaline phosphatase. In 24 percent of the patients with normal values for enzymes and no clinical evidence of bone disease the scan showed abnormalities which were proved to be metastatic lesions.[33]

Shafer and Reinke[34] carried out studies in 110 patients with cancer of the prostate; 77 had normal bone scans and after two years there was no evidence of skeletal involvement. However, in 18 patients of this group there originally was a rise

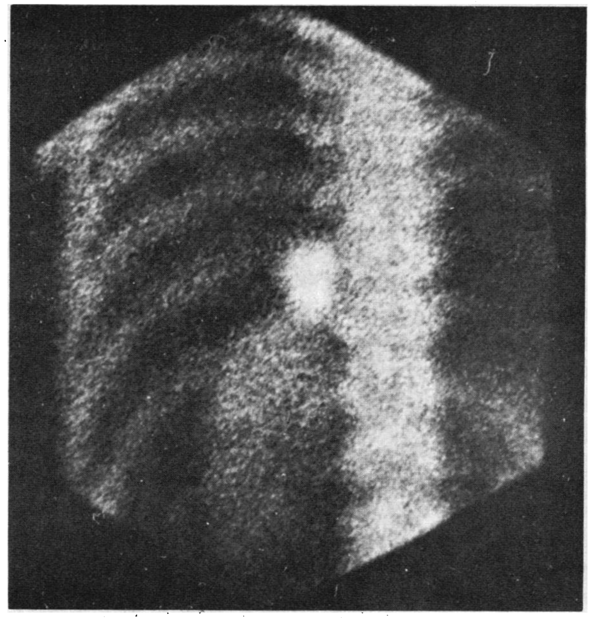

Figure 5.—Spot view showing focal uptake of methylene diphosphonate labeled with technetium 99m between ribs on the left side. This was subsequently proven to be metastatic osteogenic sarcoma in the lung.

in levels of alkaline phosphatase and in 12 patients an elevation in levels of acid phosphatase. In the 37 patients with abnormal scans due to metastases, only 25 had abnormal radiograph results, 20 had abnormal alkaline phosphatase levels and 18 had elevated acid phosphatase levels. Pistenma and co-workers[21] found that acid phosphatase did not help differentiate between those patients with and those patients without metastases to the bone.

The bone scan is the most sensitive test for detecting metastatic lesions of the bone in patients with cancer of the prostate and should be part of the evaluation in each patient.

Miscellaneous Tumors

Williams and associates[35] compared skeletal scintigraphy, plain radiographs and serum alkaline phosphatase in 100 patients with cancer of the lung. In this group 56 patients had no evidence of metastases after 18 months follow-up or at the time of death. Bone scans and radiographs were normal in all of these cases. The bone scans were abnormal in 37 of 44 cases in which metastases eventually appeared; and the scans were abnormal in seven cases in which radiographs were normal and there was no bone pain. It is interesting that six of the seven scans giving false-negative findings were in patients with oat-cell carcinoma. Hypertrophic pulmonary osteoarthropathy appears as increased linear uptake of radioactivity in the edge of long bones, and is most commonly associated with primary cancer of the lung[36,37] but can be found in other diseases.[38]

Hatfield and associates[39] found that only one patient of 16 with pancreatic carcinoma had bone metastasis detected on scan; and in their review of the literature they found autopsy or radiographic evidence of metastases in only 5 percent of 2,155 cases. Similarly Feldman and Plonk[40] found a low incidence of bone metastases in patients with midgut carcinoid tumors. Nevertheless, the 5 percent incidence of bone metastases in patients with carcinoma of the colon and rectum has been reached without bone scans and is most likely an underestimate.[41]

Of 99 patients with urogenital cancer there were abnormal scans in 59; in 52 of the 59 there were abnormal radiographs, but in an additional 11 of the 99 patients the scan showed more extensive involvement than the radiograph.[42]

Osteogenic Sarcoma

Primary bone tumors appear as expansile areas of increased uptake most frequently in the metaphyseal region of long bones such as the tibia and the femur. Metastatic lesions, even those in soft tissues such as lymph nodes and lungs,[43-46] may show active uptake of the bone scanning agents (Figure 5).

Solitary Hot Lesion on Bone Scan

Most bone scans are done to determine the presence of metastatic lesions in patients with known primary cancer. A problem often encountered is the finding of a solitary abnormality in contrast to mutiple lesions. Corcoran and coworkers[47] found this in 171 (15 percent) of 1,129 patients with nonskeletal primary cancer. A definite cause for the scan abnormality was found in 90 cases and 58 cases (64 percent) were due to metastatic disease. In a retrospective study of 861 bone scans, 63 (7.3 percent) showed a solitary lesion; 30 of these 63 were in patients with known primary cancer, and a diagnosis of the scan abnormality was made in 21 of these 30 patients.[48] Only four lesions (20 percent) were metastatic, and the remaining 17 were benign lesions of the bone discovered serendipitously. However, none of these patients had cancer commonly associated with spread to the skeleton, and several patients died of cancer before the causes of the bone scan abnormality could be deter-

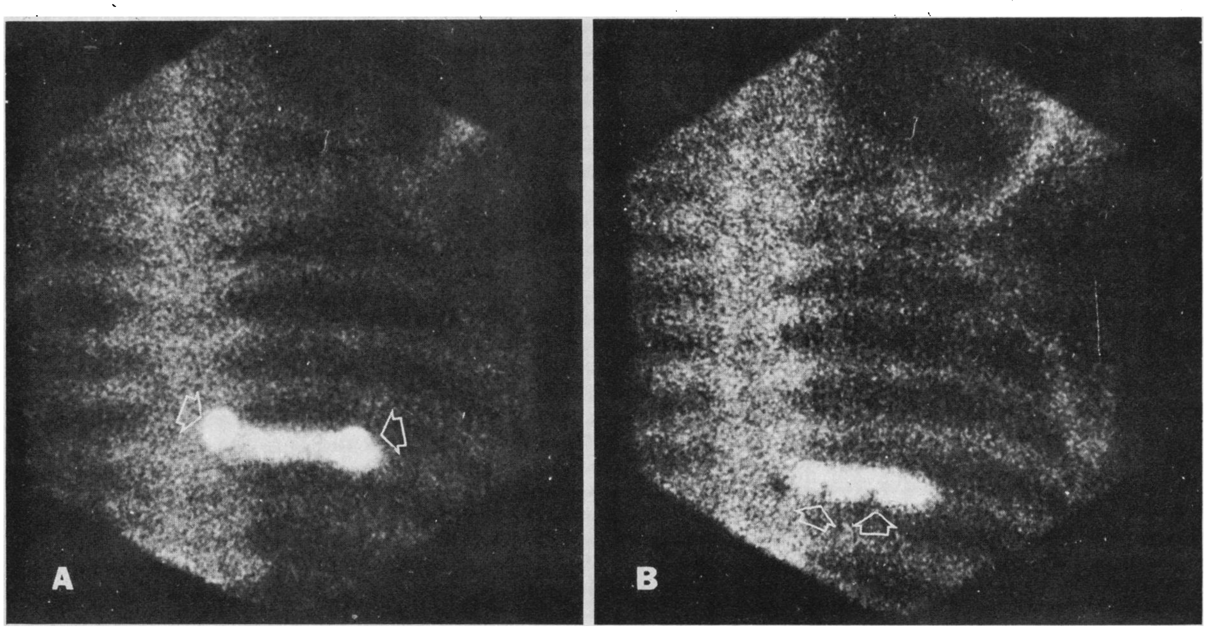

Figure 6.—A rib abnormality which was the solitary lesion on scan in a 57-year-old man with cancer of the prostate. **A**, technetium markers (shown by arrows) were used to position the lesion. Skin marks were then placed in the exact site of the technetium 99m markers as a guide for biopsy. If this technique is employed, great care must be taken to ensure that the patient is in exactly the same position for biopsy as for the scan. **B**, lead markers, which appear as small photopenic areas indicated by arrows, were placed over the abnormal rib. When lesions are marked in this fashion a standard radiograph will then define the exact site of the lesion. Ribs are not easy to count on scan, because the 1st and 12th ribs may be difficult to identify.

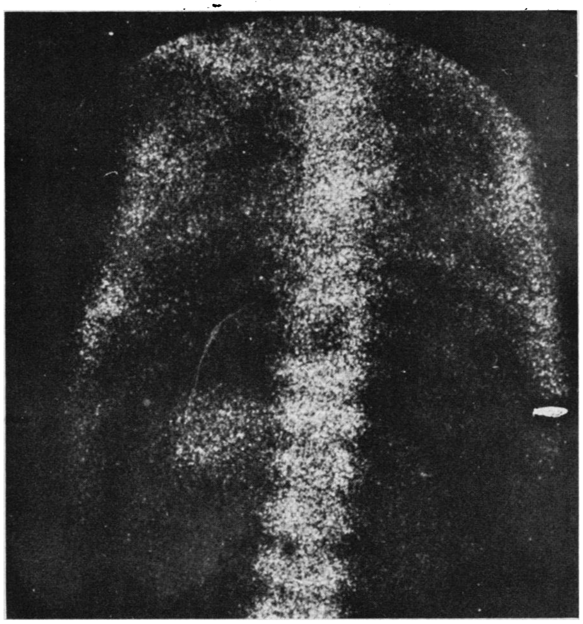

Figure 7.—Photon deficient areas in the spine of an 18-month-old child with metastatic neuroblastoma. The primary tumor shows hyperconcentration of the bone scanning agent.

mined. Therefore the 20 percent figure may be somewhat low.

Rather than be discouraged with scans because of the low incidence of malignancy shown in solitary bone lesions (20 percent to 64 percent), clinicians should accept the fact that scans are sensitive but not specific. A false-negative scan, a normal scan with radiological or clinical evidence of cancer, is rare (probably less than 2 percent) but many benign lesions of the bone will be shown and may be difficult to differentiate from metastatic lesions. Frequently, the position of the abnormality (in a joint, for example), the clinical history or a specific radiograph will define the exact nature of a solitary lesion. A single bone scan abnormality with normal radiographic results should be viewed with suspicion for neoplasm, and close clinical, scintigraphic or radiological follow-up studies would be advisable. Figures 6A and 6B show a single rib lesion in a patient with prostate cancer; the x-ray films in this case showed no abnormalities. Prostate cancer was found on a biopsy specimen of the bone. The figure also shows two methods of marking the exact position for biopsy.

Tofe and co-workers,[49] in an analysis of 1,143 whole body scans from various institutes, found single abnormalities in 4 percent of the skulls and 9 percent of the extremities. Half of the skull lesions and 63 percent of the single extremity lesions were found in patients with primary cancer of the breast, lung or prostate. Although the true incidence of cancer in these lesions was not defined, the findings emphasize two facts: first, the importance of obtaining whole body skeletal scintigrams, and second, the need to view with considerable respect any bone scan abnormality in patients with tumors in the breast, lung or prostate.

Abnormalities Appearing as Cold Areas

Most pathologic conditions of bone, such as tumors, infection or trauma, appear more intense than normal bone on a scan because there is a greater concentration of the radiopharmaceutical agent in, or around, the lesion. It is now being recognized with increasing frequency that lesions can also appear less intense. Metastasis,[50-53] sickle cell infarction,[50,52] benign tumors,[54] osteomyelitis and Perthes disease have been described as causes of cold areas. (The last two disorders are discussed more fully in appropriate sections.) Figure 7 shows cold spinal lesions in an infant with metastatic neuroblastoma.

The most probable causes of this finding are (1) the lesions are predominantly osteolytic; (2) the underlying pathologic condition causes reduced blood flow to the area; (3) the specific lesion causes less reactive new bone formation, or (4) any combination of these. Although the finding is uncommon, clinicians should be aware of the possibility and aware that *cold* lesions surrounded by normal bone are harder to see than *hot* lesions.

Summary of Bone Scan in Patients with Malignant Disease

Bone scintigraphy is a highly sensitive test for diagnosing the presence of metastatic lesions of bone, particularly in patients with primary cancer of the breast or prostate. It is useful preoperatively or perioperatively to determine the need for additional therapy and to follow sequentially the stability, progression or regression of disease. The scan has a considerable role in diagnosing cancer of the lung and genitourinary and colorectal areas, and a lesser role in diagnosing cancer of the pancreas. Provided surgical staging with bone marrow biopsy is undertaken in patients with Hodgkin disease and non-Hodgkin lymphoma, the major role of bone scan in these diseases is to

TABLE 1.—*The Ratio of Bone to Soft Tissue Radioactivity in Three Disorders*

Patients Studied	*Ratio of bone/soft tissue radioactivity at 4 hours*
Normal	4.05 (±0.69)
Primary hyperparathyroidism	3.76 (±0.26)
Renal osteodystrophy	6.29 (±1.6)
Osteomalacia	6.06 (±1.85)

detect patients in whom there are relapses localized in the bone or marrow.

Metabolic Bone Diseases

This section deals with primary hyperparathyroidism, osteomalacia and renal osteodystrophy (secondary hyperparathyroidism). Frequently bone scans show a characteristic pattern, especially in osteomalacia.[55] The characteristic features, which may not all be present in one patient, are a subjective impression of increased bone uptake of tracer, beading of the costochondral junction, increased activity in the calvarium and mandible, faint renal images and prominent (tie) sternum and pseudofractures. These findings have been described individually, or in combination, by other investigators.[56-58]

Investigators have analyzed the information by measuring plasma radioactivity (at specific times after injection of the bone scanning material), whole body retention, urinary outputs, and ratio of bone to soft tissue radioactivity. Using the data from Fogelman and co-workers,[59] the ratio of bone to soft tissue radioactivity in different disorders is shown in Table 1. The results in cases of primary hyperparathyroidism are not different from normal findings, and although patients with osteomalacia and renal osteodystrophy have a higher ratio of bone to soft tissue radioactivity than do patients without the diseases, there is considerable overlap.

Krishnamurthy and associates[60] carried out studies in 12 patients with hyperparathyroidism by using bone scans, blood clearance of the radiopharmaceutical agent, urinary excretion of the radiopharmaceutical agent and standard radiographs. In seven of the 12 patients there were abnormal scans. These investigators could not differentiate, on the basis of blood clearance, between patients with primary hyperparathyroidism and patients without disease. Wiegmann and associates[61] found that 11 of 20 patients with primary hyperparathyroidism had normal bone to soft tissue ratios, whereas five patients with secondary hyperparathyroidism could be differentiated from persons without disease.

In summary, in patients with well established metabolic bone disease the scan may show a characteristic pattern which should not be confused with that of metastatic disease. Earlier cases may not be easy to recognize and additional tests on blood and urine to determine the rate of clearance of the radiopharmaceutical agent might be helpful in osteomalacia and secondary hyperparathyroidism. This is not the case in primary hyperparathyroidism, which may be difficult to diagnose on the basis of radionuclide studies.

Paget Disease

In Paget disease of the skeleton, bone scans frequently have a characteristic appearance.[62,63] Entire bones such as the femur, tibia and ilium appear thicker and show intense uptake of the radiopharmaceutical agent. This is most likely due to increased flow of blood to diseased bones.

In mild cases, biochemical results including alkaline phosphatase and urinary hydroxyproline may be normal, though the bone scan clearly delineates abnormal areas.[64] Moderately severe cases can be diagnosed clinically, biochemically and by scanning. It was hoped that serial scans or analysis of the bone scan, including evaluation of blood clearance and urinary excretion of the radiopharmaceutical agent, would provide an accurate method of evaluating the response of the disease to therapy (such as with thyrocalcitonin). This is the case in patients with a mild form of the disease, but not in moderate or severe cases.[64]

Osteomyelitis

Early diagnosis of osteomyelitis is important so that destruction of bone and septic metastasis can be prevented. Radiographic changes may not occur for ten days to several weeks after the onset of the disease, and any test that directs physicians' attention to an abnormal site at an earlier time is a great advantage. Bone scintigraphy is a sensitive method of detecting osteomyelitis by showing increased uptake of radiopharmaceutical agents in the region of bone abscess.

Duszynski and co-workers,[65] using bone scans, diagnosed the disease correctly in 18 of 19 patients who subsequently were shown to have osteomyelitis. In only one case in this group were the abnormalities not shown on a radiograph. In another series of 19 patients with proven osteo-

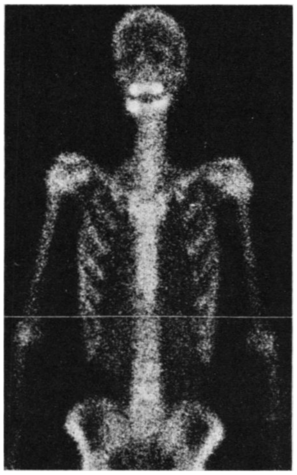

Figure 8.—Anterior view of head and torso in a patient with Hodgkin disease which shows intense uptake in maxilla and mandible resulting from a severe dental disease with apical abscesses.

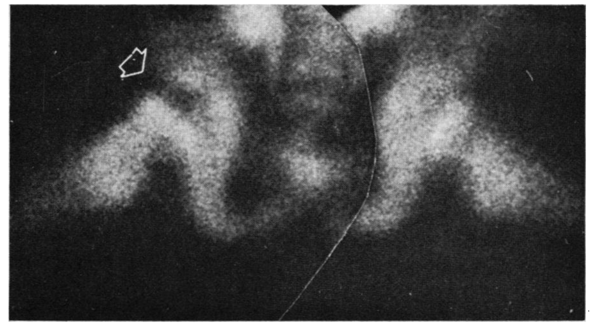

Figure 9.—Spot view of hip joints in an 8-year-old showing Perthes disease.

myelitis, the bone scans showed the abnormal sites in 16 cases. In ten of the 16 cases roentgenograms showed no abnormalities.[66] Kempi and van der Linden[67] found scans to be positive in all of 14 cases in which patients were thought to have osteomyelitis; in seven cases the roentgenograms showed abnormalities at the time of scanning, and in the remainder there were abnormal findings on roentgenograms 1 to 20 weeks after the scintigrams were done. Osteomyelitis found in unusual sites such as the mandible[68,69] or sacroiliac regions[70] can be detected. Figure 8 shows the scan appearance of apical dental disease. Handmaker and Leonards[71] showed that the scan may be abnormal within 24 hours of the appearance of symptoms; however, this raises an important question regarding the meaning of normal scan results in cases of suspected osteomyelitis. In most series there is a small number of patients in whom the scan does not show abnormal uptake; in two studies discussed above, this occurred in one of 19 patients[65] and in three of 19 patients.[66] Indeed, there are reports of cases in which osteomyelitis appears as a cold area.[72-75] Clinicians should be aware of the fact that osteomyelitis does not always appear as a hot area. Most likely in the early phase of osteomyelitis, acute inflammation of the bone and marrow causes thrombosis of arterioles and capillaries, and reduces the blood flow to the area. With reduced blood flow, a reduced amount of the radiopharmaceutical agent is deposited, and a normal or cold area appears on the scan. A model of osteomyelitis in rabbits showed similar findings.[76] What should be done in the small number of patients in whom osteomyelitis is suspected, when scans and radiographs are normal? Probably the best approach is to use a gallium 67 scan; results are almost always abnormal in these circumstances. Because the bone scan is usually abnormal and because of the higher radiation dose and poorer resolution of ^{67}Ga, it is unnecessary to use ^{67}Ga scans in all cases. ^{67}Ga scans are preferable to conventional bone scintigraphy for determining whether or not the infection has resolved, because the bone scan may remain abnormal for weeks or months. In most patients, careful clinical judgment and evaluation of leukocyte counts and differentials, and the erythrocyte sedimentation rate, may be more satisfactory in determining resolution—and they are less expensive. An alternative, but not yet fully evaluated approach, would be to use autologous leukocytes labeled with indium 111.

Uncommon chronic forms of osteomyelitis, such as tuberculosis[77] and leprosy,[78] may be noted on scans as areas of increased uptake of radiopharmaceutical agents. Scans also have been found useful in diagnosing osteomyelitis in drug abusers.[79]

Bone scintigraphy is a sensitive method of detecting osteomyelitis. Whether or not earlier diagnosis of the disease will result in a shorter period of treatment remains to be seen.

Benign and Traumatic Abnormalities

Osteonecrosis

There have been considerable data supporting the fact that bone scans are superior to standard radiographs for the early detection of osteonecrosis. If the scan is conducted at a very early stage in the evolution of the osteonecrosis, a cold avascular area will be seen. This is more frequently encountered in patients with Perthes disease than in those with steroid-induced osteonecrosis.[80] It is more likely that the scan will show increased uptake of radiopharmaceutical agents around the affected area, probably as a result of reactive bone formation.[81,82] Figure 9 shows an avascular hip in a patient with Perthes disease.

Trauma

Most cases of bone trauma are best evaluated with roentgenography; however, stress fractures are frequently not recognized on radiography until the healing phase occurs. If it is important to record the presence of a fracture—such as in troops or athletes—a bone scan is a sensitive method of showing the lesion.[83,84] Bone scans are also valuable in diagnosing and showing the extent of trauma in battered babies.[85]

Nonskeletal Abnormalities Seen on Bone Scan

A large number of nonskeletal abnormalities, both malignant and benign, concentrate bone-seeking radiopharmaceutical agents. The most important is acute myocardial infarction, and pyrophosphate labeled with technetium 99m is used commonly as an aid in making this diagnosis.[86,87] Cerebral infarct[88] and cerebral tumors[89] show positive uptake as do a spectrum of hepatic disorders including metastatic lesions of the colon,[90] amyloidosis,[91] and hepatic necrosis.[92] Primary cancer of the breast[93] and a normal breast[94] can occasionally show increased concentration This list is not complete and readers are referred to the reviews by Fratkin[92] and Oren and Uszler.[95]

Renal Findings on Bone Scan

Of bone scanning agents, 50 percent to 60 percent are cleared by the kidneys and excreted in the urine; as a result, it is not unusual for renal or bladder lesions to be detected. Therefore, it is important for these structures to be carefully evaluated when a bone scan is read.

In an analysis of 1,711 bone scans, renal abnormalities were found in 247.[96] In all, 52 were graded as significant and included polycystic disease and renal cell carcinoma. Hydronephrosis, hydroureter, cysts, carcinoma and nonfunctioning kidney were among nine abnormalities found in 52 patients.[97] Vieras and Boyd[98] found that only one of 751 normal-appearing kidneys on bone scan had a radiographic renal abnormality, and when the radionuclide image was abnormal the result was confirmed radiographically in 84 percent of patients. Unexpected renal findings have also been described by Mandel and associates[99] and rare renal malformations, such as horseshoe kidney, have been encountered.

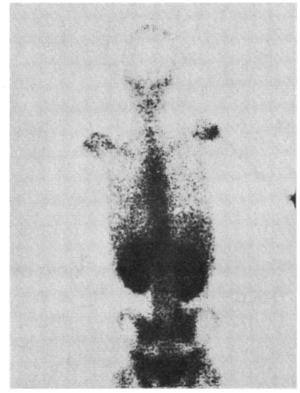

Figure 10.—Intense uptake of bone-seeking radiopharmaceutical agent in the kidneys of a child who had received antitumor chemotherapy.

Renal carcinoma usually apears as a filling defect on the scan[100] but there are reports of cases in which there is increased uptake in the tumor,[101,102] a finding that has not been adequately explained.

Lutrin and co-workers[103] have described intense uptake of bone scanning agents in the kidneys of children receiving antitumor chemotherapy (Figure 10). This association was noted in children who had received cyclophosphamide, doxorubicin hydrochloride and vincristine. The cause of this finding has not been defined, but it is probably related to direct toxicity of the antitumor drugs in renal tubular cells.

Artifacts on Bone Scintigram

One half of the x-rays emitted by technetium 99m are attenuated by 5 cm of tissue. Denser materials overlying the patient such as a silicone breast prosthesis, belt buckle, hip flask or pacemaker may conceal bones and pathologic conditions may be overlooked.[104] Occasionally barium in the bowel[105] or even a large meal[106] can cause a photopenic area. Contamination with urine containing radioactivity may produce a false positive lesion. The nuclear specalist should be responsible for evaluating each scan before the patient is discharged from the department. It may be necessary to correlate clinical information, review past history of trauma, obtain spot views of abnormal areas and even to do some detective work to explain each abnormality on the scan.

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